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# Inhaled corticosteroid dose-response in asthma: should we measure inflammation?

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**Keywords**

Asthma; inhaled corticosteroid; dose-response; inflammation; symptoms; spirometry; FeNO; airway hyper-responsiveness; ECP; blood eosinophils.

**Abbreviations**

| | |
|---|---|
| AHR | Airway hyper-responsiveness |
| ANOVA | Analysis of variance |

| | | |
|---|---|---|
| 23 | AQLQ | Asthma Quality of Life Questionnaire |
| 24 | ATS | American Thoracic Society |
| 25 | BDP | Beclomethasone Dipropionate |
| 26 | BTS | British Thoracic Society |
| 27 | Bud | Budesonide |
| 28 | CFC | Chlorofluorocarbon |
| 29 | CI | Confidence interval |
| 30 | CIC | Ciclesonide |
| 31 | DD | Doubling dilution |
| 32 | DDD | Doubling dilution difference |
| 33 | ECP | Eosinophilic cationic protein |
| 34 | Eos | Eosinophils |
| 35 | $FEF_{25-75}$ | Forced expiratory flow between 25-75% of forced vital capacity |
| 36 | FeNO | Fractional exhaled nitric oxide |
| 37 | $FEV_1$ | Forced expiratory volume in 1 second |
| 38 | FP | Fluticasone propionate |
| 39 | GMFD | Geometric mean fold difference |
| 40 | HFA | Hydrofluoroalkane |
| 41 | Hist $PC_{20}$ | Provocative concentration of histamine causing 20% fall in $FEV_1$ |
| 42 | ICS | Inhaled corticosteroid |
| 43 | LABA | Long-acting beta-2 agonist |
| 44 | Mann $PD_{10}$ | Provocative dose of mannitol causing a 10% fall in $FEV_1$ |

| | |
|---|---|
| Mann $PD_{15}$ | Provocative dose of mannitol causing a 15% fall in $FEV_1$ |
| MCID | Minimum clinically important difference |
| Meth $PC_{20}$ | Provocative concentration of methacholine causing 20% $FEV_1$ fall |
| %Pred | Percentage of predicted |
| Ppb | Parts per billion |
| RCT | Randomised controlled trial |

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## Introduction

Asthma is a heterogeneous chronic inflammatory disease of global importance[1], which places a significant burden both on individual patients and on health care services, where many patients remain inadequately treated[2, 3] with an ongoing attendant mortality[4]. The concept of achieving 'total asthma control'[5] is important for reducing the future risk of exacerbations[6-8]. It is therefore imperative that we have robust procedures for accurate diagnosis, measurement of severity, prediction of future risk, along with appropriate personalised treatments to achieve this goal. Nevertheless, present guidelines for the identification and treatment of asthma merely include symptoms and lung function measurements[5, 9]. The Royal College of Physicians' recent National Review of Asthma Deaths report[4] found that only 39% of patients who died were actually labelled as having 'severe' asthma according to current guidelines, with the remainder therefore labelled as 'mild' or 'moderate', suggesting we may not be accurately identifying those at greatest risk.

Measurement of inflammatory outcomes has improved our understanding of asthma, evolving personalised treatment. Studies have shown that titrating steroid therapy against inflammation may improve outcomes such as exacerbation rates[10-12]. For example in one primary care based study titrating inhaled corticosteroid dose against mannitol challenge verses a reference strategy, resulted in a 27% significant reduction in mild exacerbations but no difference in severe exacerbations[11]. Similar findings were observed in another study using methacholine challenge[13]. Green et al. demonstrated this by titrating

steroid treatment against sputum eosinophil counts, resulting in significantly fewer severe exacerbations compared to standard guideline driven treatment[10]. It is interesting that this was achieved with no difference in overall mean dosage of ICS between the two groups, suggesting that for the individual, any steroid titration was performed at the right time for them when their levels of inflammation were greater. However, other studies have suggested a more muted response to inflammatory steroid titration in unselected asthmatic patients[14, 15].

Price et al. demonstrated retrospectively, in a primary care cohort, that asthmatic patients with higher blood eosinophil counts fared worse in terms of experiencing more severe exacerbations and poorer asthma control[16]. Moreover, eosinophilic inflammation may be masked when using a long-acting beta-2 agonist (LABA) as a steroid-sparing agent[17, 18]. Sputum and blood eosinophilia in asthma have both been separately shown to predict loss of asthma control and increased exacerbation rates[6, 19, 20]. This is also true of fractional exhaled nitric oxide (FeNO) levels[21] and airway hyper-responsiveness (AHR)[6], the latter being largely driven by airway inflammation[22]. It is therefore logical that one might wish to control inflammation over and above simply controlling symptoms and lung function – much like controlling asymptomatic hypertension to prevent subsequent cardiovascular sequelae. This is relevant given lung function and lack of symptoms may be deemed normal despite the possibility of an ongoing underlying inflammatory process[23].

We performed a post-hoc pooled analysis of data from four previously published randomised controlled trials (RCTs) where inhaled corticosteroid (ICS) dose titration was used in a prospective manner. Outcome measurements included symptoms, lung function, inflammation and AHR. We then analysed the dose-response relationship to ICS for these outcomes to identify where incremental ICS dosing provides the greatest impact, and thus likely to be most informative when titrating a given individual's treatment to achieve optimal or total asthma control.

## Methods

*Patients*

Male and female mild-moderate, non-smoking, persistent asthmatics aged 18-65 years receiving ≤1000μg/day ICS, i.e. expressed as a reference dose of large particle beclomethasone dipropionate (BDP) equivalent dose, were recruited to each of four RCTs[11, 24-26]. For example, large particle HFA-fluticasone 200ug or small particle HFA-beclomethasone 200ug would be equivalent to large particle HFA-BDP 400ug. Their post-run-in baseline measurements are presented in Table 1. Further detailed inclusion and exclusion criteria can be found in each of the reported trials.

*Study Design*

We performed a post-hoc analysis using data from 4 RCTs[11, 24-26], each comprising a component where the effects of ICS dose ramp increments were examined on a variety of outcomes including: spirometry, FeNO, AHR including both indirect (mannitol) and direct (methacholine, histamine) challenges, asthma symptoms, serum eosinophilic cationic protein (ECP), and blood eosinophil count (Eos). Briefly, one study used large particle hydrofluoroalkane (HFA)-fluticasone propionate (FP) using FeNO as the primary outcome[24]: with an ICS-free run-in, followed by either 200μg or 800ug BDP equivalent. A second study titrated small particle HFA-ciclesonide against mannitol AHR versus titration using standard British Thoracic Society (BTS) guidelines[11]: patients

were selected from both arms of this study where there was an appropriate dose ramp (i.e. BDP equivalent 200-800µg/day). A third study used methacholine AHR as the primary outcome comparing large particle (HFA) and chlorofluorocarbon (CFC) formulations of budesonide[25]: within the HFA arm there was an ICS free washout followed by 200µg/day or 800ug/day BDP equivalent. The fourth study examined whether propranolol was useful as an ICS sparing agent[26], with histamine AHR the primary outcome: the control arm was effectively a dose ramp between small particle HFA-beclomethasone at BDP equivalent doses of 200µg/day or 800ug/day.

*Measurements*

Extended detail of measurements can be found in each parent study. Briefly, spirometry was measured using a SuperSpiro spirometer (Micro Medical Ltd.) according to American Thoracic Society (ATS) guidelines[27]. Exhaled tidal nitric oxide was measured according to ATS recommendations[28] using a NIOX analyser (NIOX® Nitric Oxide Monitoring System, Aerocrine AB) prior to other pulmonary function measures. Mannitol challenge was performed as previously described[29] with a dry powder inhaler (Aridol; Pharmaxis Ltd) using cumulative dose increments up to 635 mg. Histamine for bronchial challenge was dispensed via nebulized solution with doubling concentrations of histamine from 0.3125mg/ml to 40mg/ml. Methacholine challenge was performed using the five-breath dosimeter technique in accordance within ATS recommendations[30]. Peripheral blood eosinophils were measured using the Sysmex XE2100 Hematology auto-analyser. Serum ECP was measured in duplicate using a

UniCAP system (Phadia) with a coefficient of variation of 3%. For symptoms, 3 studies[11, 24, 26] included the mini-Asthma Quality of Life Questionnaire (AQLQ, symptom component), where a mean score of 7 indicates no symptoms, and <7 indicates progressively worse symptoms. In the fourth study[25], the following rating scales were used: 0, no asthma symptoms; 1, mild symptoms (easily tolerable); 2, moderate symptoms (interferes with normal activities/sleep); and 3, severe (prevents normal activities/ sleep). The total asthma symptom score was a mean of both morning and evening symptom scores.

*Statistical Analysis*

All data were initially assessed for normality of distribution, with non-Gaussian distributions logarithmically transformed to enable parametric analyses. For the primary analyses, examining for any change within a given outcome measure following an ICS dose ramp, arithmetic means of the difference within each ICS dose ramp were calculated for outcomes with the same parametric measure across all 4 studies. Geometric mean fold differences were calculated for changes in outcomes that were either non-parametric, or with different measurements between the studies in order to standardize any changes (e.g. bronchial challenges). Analyses of variance (ANOVA) with Bonferroni correction were also used to compare the differences between dose ramp responses, and each individual dose mean. Multiple linear regression analyses, using both forward stepwise and non-hierarchical introduction of predictors, were also employed to examine for any confounding effects of biological covariates on the

main outcome measures. Statistical significance for all comparisons was set at $P<0.05$. Statistical analyses were performed using IBM SPSS version 22.

*Ethics*

The East of Scotland Research Ethics Service granted ethical approval for all studies (Refs: NFB/FB/192/03[11], 09/S0501/52[24], 11/ES/0031[26], 08/S1402/14[25]). All patients provided written informed consent. The studies were registered at ClinicalTrials.gov: NCT00667992[25], NCT00995657[24], NCT01216579[11], NCT01544634[26].

## Results

We included 121 evaluable participants from the parent studies (Table 1). Ciclesonide patients were approximately 10 years older. Patients had generally preserved pulmonary function, overall mean $FEV_1$ 85.1% predicted, and had mild symptoms. FeNO was higher in the Fluticasone group due to the inclusion criteria of that study. Despite the different bronchial challenges, their figures all indicated a moderate-severe degree of AHR. Patients had been receiving similar ICS doses prior to study inclusion, mean 420µg/day BDP equivalent.

For pulmonary function, there were small but statistically significant changes seen within the 0-200µg dose ramp for both $FEV_1$ and $FEF_{25-75}$ (Table 2, Figure 1), with a 3.3% (95%CI 2.0,4.7) rise in $FEV_1$ (P<0.0001), and 4.6% (95%CI 2.4,6.9) rise in $FEF_{25-75}$ (P<0.0001). However, there was a plateau in response at 200-800µg for both these measures. There were also statistically significant within-group improvements for symptom scores (Figure 1) at all dose ramps, but with less improvement within the 200-800ug dose ramp: along with a significant difference (P=0.01) when comparing responses between 0-800µg vs. 200-800µg, i.e. again indicating a plateau in response.

For inflammation, significant improvements in FeNO were seen across all ICS dose ramps (Table 2, Figure 2a), with clear evidence of dose separation (Table 2). Improvements were more pronounced in the subgroup with baseline values of FeNO≥25ppb (Figure 2b), and significantly different compared to the subgroup with baseline values of FeNO<25ppb. Serum ECP did not improve with

168 the low dose ramp 0-200μg (Table 2, Figure 2c), rather requiring the higher ICS
169 dose to achieve significant within-group improvements between 0-800μg
170 (P=0.002) and 200-800μg (P=0.0002); again the dose ramp responses were
171 significantly different between 0-200μg and 200-800μg (P<0.05). Finally there
172 were significant within group improvements for blood Eos across all dose ramps
173 (Table 2, Figure 2d), where Eos also continued to fall significantly as the ICS dose
174 increased: 370cells/μL (95%CI 280,450) at 0μg, to 250cells/μL (95%CI 200,300)
175 at 800μg, P=0.03.
176
177 Significant within group changes were seen across all dose ramps for AHR
178 (Figure 3a). The greatest improvement was in the 0-800μg group at 1.35
179 doubling dilutions (DD) (95%CI 1.06,1.63), P<0.0001, with further significant
180 improvement in the 200-800μg group amounting to 0.7DD (95%CI 0.43,0.96),
181 P<0.0001. Significantly greater improvements were seen when AHR was
182 separated into indirect (mannitol) versus direct challenges (histamine,
183 methacholine), particularly at the lower dose ramp 0-200μg, 1.64DD (95%CI
184 0.94,2.35) indirect vs. 0.65DD (95%CI 0.40,0.89) direct, P=0.015 (Figure 3b).
185
186 Multiple linear regression analyses were performed on four main outcome
187 measures: change in $FEV_1$ (% predicted); change in symptom scores; change in
188 FeNO levels; and AHR doubling dilution differences. The covariates used as
189 predictors of these outcomes were: age; gender; and ICS dose ramps (i.e. 0-
190 200μg, 0-800μg and 200-800μg). ICS dose ramps significantly predicted all
191 outcomes in keeping with our previous findings: change in $FEV_1$% (p<0.001);
192 change in symptoms (p=0.012); change in FeNO (p<0.001); and change in AHR

193 (p=0.003). Age was not a significant predictor of any outcome measure. Gender
194 was a significant predictor of change in symptom scores (p=0.001), suggesting
195 male gender correlated with a greater improvement in symptoms, but gender
196 did not significantly impact on changes in $FEV_1$%, FeNO or AHR.
197

## Discussion

In the present study we have demonstrated that incremental ICS dosing in persistent asthma leads to small improvements in both pulmonary function and symptoms, which then reaches a plateau above low doses. We have also found that the same ICS dose ramps reveal further room for improvement in both inflammatory outcomes and AHR, when using higher ICS doses up to 800µg/day (beclomethasone equivalent).

The BTS guidelines describe the goal of total (or optimal) asthma control as comprising no symptoms day or night, normal lung function and no exacerbations[5]. Unfortunately, it has been shown that patients are not good at recognizing when their asthma is not controlled[3]. Furthermore, lingering underlying inflammation may be present[23], and until this is treated, symptoms may take many months to become completely normal[31]. We have shown here that patients who have only mild pulmonary function and symptom impairment respond optimally to low doses of ICS for these outcomes. Pointedly, however, the 3.3% rise in $FEV_1$ for 0-200µg equated to a mean of 98ml (95%CI 57,140), which is less than the putative minimal clinically important difference (MCID) of 230ml in asthma[32]. Moreover, for symptoms, the geometric mean fold difference of 0.94 (95%CI 0.90,0.98) in the 200-800µg group equates to around a 6% improvement. For the mini-AQLQ, for example, 6% represents a change of around 0.4, where the MCID is 0.5[33]. The low dose plateau of symptoms and lung function have been well documented[34-37]; for example, Masoli et al. showed no further improvement in pulmonary function beyond 200µg day of FP[37]. Indeed

Pauwels et al. in the FACET study[38] showed a dose response on exacerbations but not $FEV_1$ comparing 200µg/day vs. 800µg/day of budesonide. Yet we still largely base our asthma management on these two outcomes, in addition to reliever use, particularly for mild to moderate persistent asthma; thus limiting further potentially appropriate ICS escalation.

We have demonstrated room for further improvement in multiple markers of inflammation (FeNO, serum ECP and blood Eos) and AHR with higher doses of ICS, despite ~~the~~ an apparent plateau in symptoms and lung function. The presence of ongoing airway inflammation in asthma has been shown to predict not only future exacerbations[21, 39], but also loss of asthma control[20] upon reduction or removal of ICS treatment. Furthermore, this has been demonstrated using a variety of inflammatory outcomes including sputum Eos[20, 39], blood Eos[16], FeNO[21] and AHR[11, 13]. Moreover, targeted ICS therapy towards inflammatory outcomes has been shown to reduce the rate of exacerbations[10], or reduce the overall steroid dose required for total control[12]. We have found that while most improvement in FeNO occurs with low dose ICS, there is still a further dose response to higher ICS doses, particularly in patients who exhibit a high baseline FeNO≥25ppb. This dose response has been shown previously, and indeed when ICS is stopped there is a rebound rise in FeNO once again[40], which alludes to a possible need for persistent over intermittent ICS therapy, or indeed non-adherence to ICS therapy[41]. Indeed, in the FeNOtype study[24] (one of the parent studies of this cohort), significant improvements in asthma control were seen in the ACQ scores, where patients moved from 'not well controlled' to 'well

247 controlled' with an ACQ <0.75, upon steroid titration that significantly reduced
248 the patients' FeNO levels.
249
250 We saw a similar pattern of response to that of inflammatory outcomes with
251 AHR to a variety of bronchial challenges, both direct and indirect. Indirect
252 challenges are more closely related to the inflammatory pathway as they invoke
253 the inflammatory response in the airway to cause bronchoconstriction[22]. This is
254 perhaps the reason we found a greater magnitude of response for AHR to
255 indirect than direct challenges, in keeping with previous studies[42, 43]. Targeting
256 ICS therapy using mannitol challenge AHR has been shown to reduce mild
257 exacerbations over and above standard guideline driven therapy[11], in line with
258 that for sputum eosinophils[10]. However, AHR can be driven by other
259 mechanisms such as airway smooth muscle hyperplasia, and airway closure
260 itself[44], and is therefore an area requiring further study with regards to
261 personalised asthma treatment[45].
262
263 There is therefore a growing body of evidence suggesting that we need to include
264 inflammatory measurements routinely to best manage patients with asthma.
265 This is problematic, not least due to the cumbersome nature of inflammatory and
266 challenge measurements that are difficult to perform in a community setting;
267 albeit measuring blood eosinophils might be part of the solution[16]. Cowan et al.
268 have suggested using a panel of inflammatory biomarkers to better enable
269 prediction of ICS responsiveness in asthma[46], but delivery of such a test remains
270 the most difficult hurdle. Even simply using the asthma control questionnaire[24]
271 itself seems to be a good predictor of future risk[8].

We believe the strengths of this study are in the cross-section of patients with mild to moderate disease that we commonly see in clinical practice; who additionally use a variety of ICS moieties. Furthermore we believe it has been helpful to study a wide variety of outcome measures, none of which have taken priority in the study design. There are significant limitations of this study due to its post-hoc nature, with relatively low numbers and our ability to only examine low to moderate, albeit commonly used, doses of small and large particle HFA-ICS. Additionally, we do not have longer-term outcome data such as any effects on exacerbation rates. The findings of this study can, therefore, only generate hypotheses for larger, longer-term prospective randomised controlled trials. We would suggest that they do indeed focus on both phenotyping patients on study inclusion, as well as examining the impact of combining measures of inflammation and AHR in addition to asthma control when titrating ICS, rather than using single outcome measures.

It is likely that when treating any individual patient in real life that the clinician needs to adopt a multifactorial approach when titrating therapy, using all of the available information in terms of exacerbations, symptoms, pulmonary function, reliever use, FENO, blood eosinophils and AHR. This is likely to have the best predictive value for any given individual in terms of tailoring appropriate ICS and adjunctive controller therapy to achieve the best long term control.

In conclusion, we have demonstrated that there may be further room for improvement in markers of inflammation and AHR, despite a seeming plateau in the dose response to ICS for both asthma symptoms and pulmonary function,

297 with small and large particle ICS HFA-formulations and doses. This points to a
298 potential unmet need of uncontrolled underlying airway inflammation in certain
299 asthmatic patients, which may be a precursor to future loss of asthma control.
300 We would like to emphasise that f~~F~~urther prospective study is however required
301 to prospectively examine this issue, with particular reference to longer-term
302 outcomes including exacerbation rates and overall asthma control and how this
303 relates to inflammatory markers.
304

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| Study Baselines | All n=121 | FP (ICS Free) n=21 | Bud (ICS free) n=72 | HFA-BDP (200µg BDP) n=16 | CIC (200µg BDP) n=12 |
|---|---|---|---|---|---|
| **Age (yr)** | 39.8 (37.2,42.4) | 36.8 | 39.6 | 37.8 | 48.7 |
| **Sex (M:F)** | 44:77 | 6:15 | 29:43 | 6:10 | 3:9 |
| **SPT allergens[§]** | 3 (2,4) | 3 (1,4) | 3 (2,3.25) | 2.5 (1,4) | 1.5 (0,3.25) |
| **SPT positivity (% patients)** | 89 | 81 | 94 | 88 | 63 |
| **$FEV_1$ (% pred)** | 85.1 (82.9,87.3) | 88.5 | 82 | 90.3 | 89 |
| **$FEF_{25-75}$ (% Pred)** | 65.7 (61.5,69.8) | 53.5 | 70.4 | 60.3 | - |
| **$FEV_1$/FVC ratio (%)** | 75.2 (73.7,76.7) | 71.2 | 75.6 | 74.6 | 80.5 |
| **FeNO (ppb)*** | 37.3 (32.3,42.6) | 72.4 | 34.7 | 29.1 | 25.4 (n=10) |
| **AHR*** | - | 102mg (57,183) Mann $PD_{15}$ | 0.72 mg/ml (0.58,0.90) Meth $PC_{20}$ | 1.31mg/ml (0.64,2.69) Hist $PC_{20}$ | 59mg (15,233) Mann $PD_{10}$ |
| **ECP (µg/L)* (n=47)** | 20.5 (15.9,26.3) | 18.6 | - | 22.4 | 21.9 |
| **Eos (cells/µL) (n=37)** | 330 (280,390) | 370 | - | 290 | - |
| **Symptom Score** | - | 5.8 (5.4,6.2) | 0.96[¶] (0.79,1.12) | 6.2 (5.9,6.5) | 6.1 (5.6,6.5) |
| **Screening ICS (BDP, µg/day)** | 420 (361,479) | 440 | 414 | 406 | 436 |

**Table 1.** Baselines post run-in at the given beclomethasone dipropionate (BDP) equivalent doses for: large-particle hydrofluoroalkane (HFA)-fluticasone propionate (FP), large-particle HFA-budesonide (Bud), small-particle HFA-beclomethasone (HFA-BDP), and small-particle HFA-ciclesonide (CIC). SPT = Skin Prick Test to common allergens. Overall means (95%CI), leftmost column. Arithmetic means (95%CI), unless stated. *Geometric mean (95%CI). [§]Median number of allergens (interquartile range). Symptom scores are the symptom component of the mini-AQLQ, except Bud. [¶]Total Symptom Score: 0-no symptoms; 1-mild; 2-moderate; and 3-severe.

| ICS BDP (µg/day) | ICS Free (a) | 200ug (b) | 800ug (c) | P-value (ANOVA) |
|---|---|---|---|---|
| **Pulmonary Function** | | | | |
| **$FEV_1$ (% pred)** | 83.4 (81.0,85.9) n=93 | 87.6[§] (85.4,89.9) n=121 | 87.9[§] (86.0,89.9) n=121 | 0.01 |
| **$FEF_{25-75}$ (% pred)** | 66.6 (62.0,71.2) n=93 | 69.6 (65.7,73.5) n=109 | 70.0 (66.1,73.8) n=109 | 0.47 |
| **Inflammatory Outcomes** | | | | |
| **FeNO (ppb)*** | 40.4 (34.7,46.9) n=93 | 26.8[#] (23.4,30.2) n=115 | 20.8[#¶] (18.8,23.1) n=115 | <0.0001 |
| **ECP (µg/L)*** | 18.7 (12.1,28.8) n=21 | 20.2 (15.3,26.5) n=47 | 13.2 (9.9,17.4) n=47 | 0.08 |
| **Eos (cells/µL)** | 370 (280,450) n=21 | 300 (240,350) n=38 | 250[§] (200,300) n=38 | 0.04 |

**Table 2**. Pulmonary function and inflammatory outcomes. Data presented as arithmetic means (95% confidence intervals) unless otherwise stated. *Geometric mean (95% CI). [§]P<0.05 vs. (a). [¶] P=0.01 vs. (b). [#]P<0.001 vs. (a).

## Figure Legends

**Figure 1**. Dose Responses for $FEV_1$ and Symptom Scores. (a) mean percentage changes (95%CI error bars) for $FEV_1$ as %predicted. (b) change in symptom scores as geometric mean fold differences (GMFDs, 95% CI error bars); scores <1 indicate improvement. Asterisk denotes significant within-group change, P<0.05. Remaining P-values compare responses between groups.

**Figure 2.** Dose-responses for inflammatory outcomes. Within-group changes (GMFDs, 95%CI) unless stated; scores <1 represent a reduction. (a) FeNO. (b) FeNO comparing baseline FeNO≥25ppb (squares) vs. FeNO<25ppb (circles). (c) serum ECP. (d) blood eosinophils, arithmetic mean (95%CI). Asterisk denotes significant within-group difference, P<0.05. Remaining P-values indicate significant between group differences; or significant differences between baseline FeNO groups within each ramp (b), P<0.05.

**Figure 3.** Dose-responses in airway hyper-responsiveness (AHR). Within-group changes expressed as doubling dilution differences (DDD). Scores >0 indicate improvement. (a) combined bronchial challenges: 0-200, n=93; 0-800, n=93; 200-800, n=120. (b) direct (circles) vs. indirect (squares) challenges: direct 0-200, n=72; direct 0-800, n=72; direct 200-800, n=88; indirect 0-200, n=21; indirect 0-800, n=21; indirect 200-800, n=32. Asterisk denotes significant within group change, P<0.05. Remaining P-values indicate significant between group differences (a), or significant differences between challenge groups within each ramp (b), P<0.05.

**Figure 1**

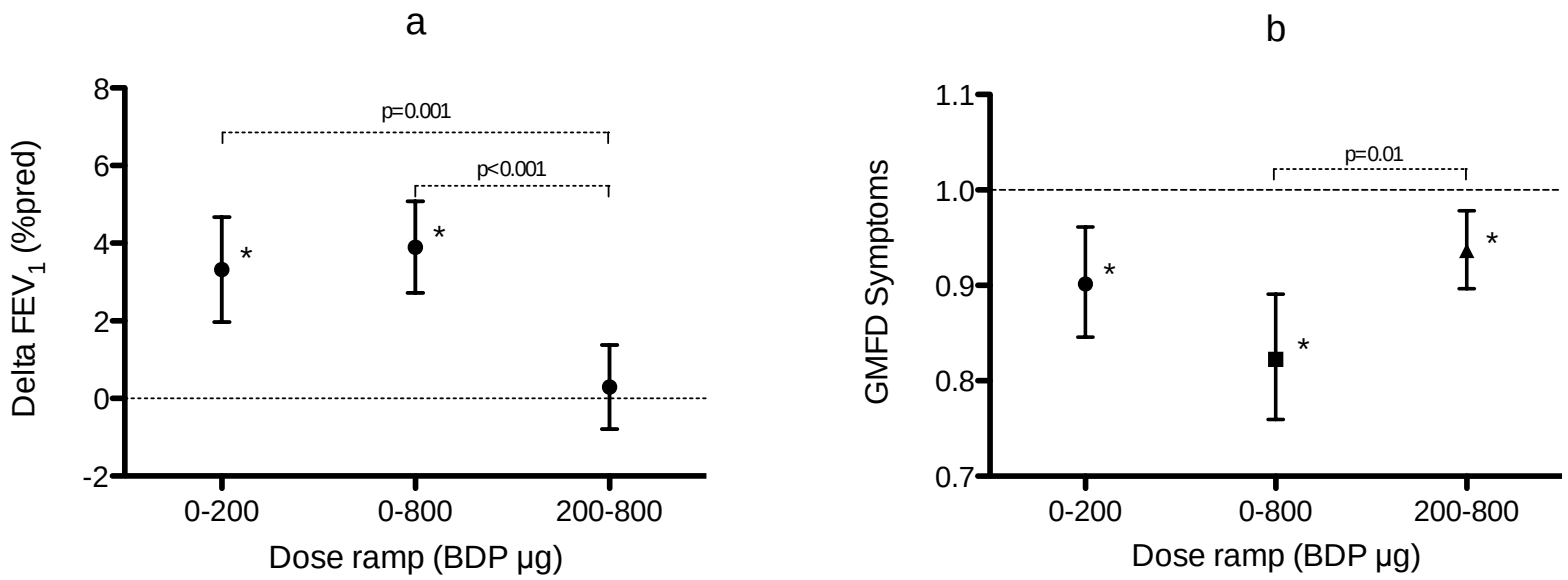

a
Delta FEV1 (%pred)
8
6
4
2
0
-2
p=0.001
p<0.001
*
*
0-200
0-800
200-800
Dose ramp (BDP µg)
b
GMFD Symptoms
1.1
1.0
0.9
0.8
0.7
p=0.01
*
*
*
0-200
0-800
200-800
Dose ramp (BDP µg)

**Figure 2**

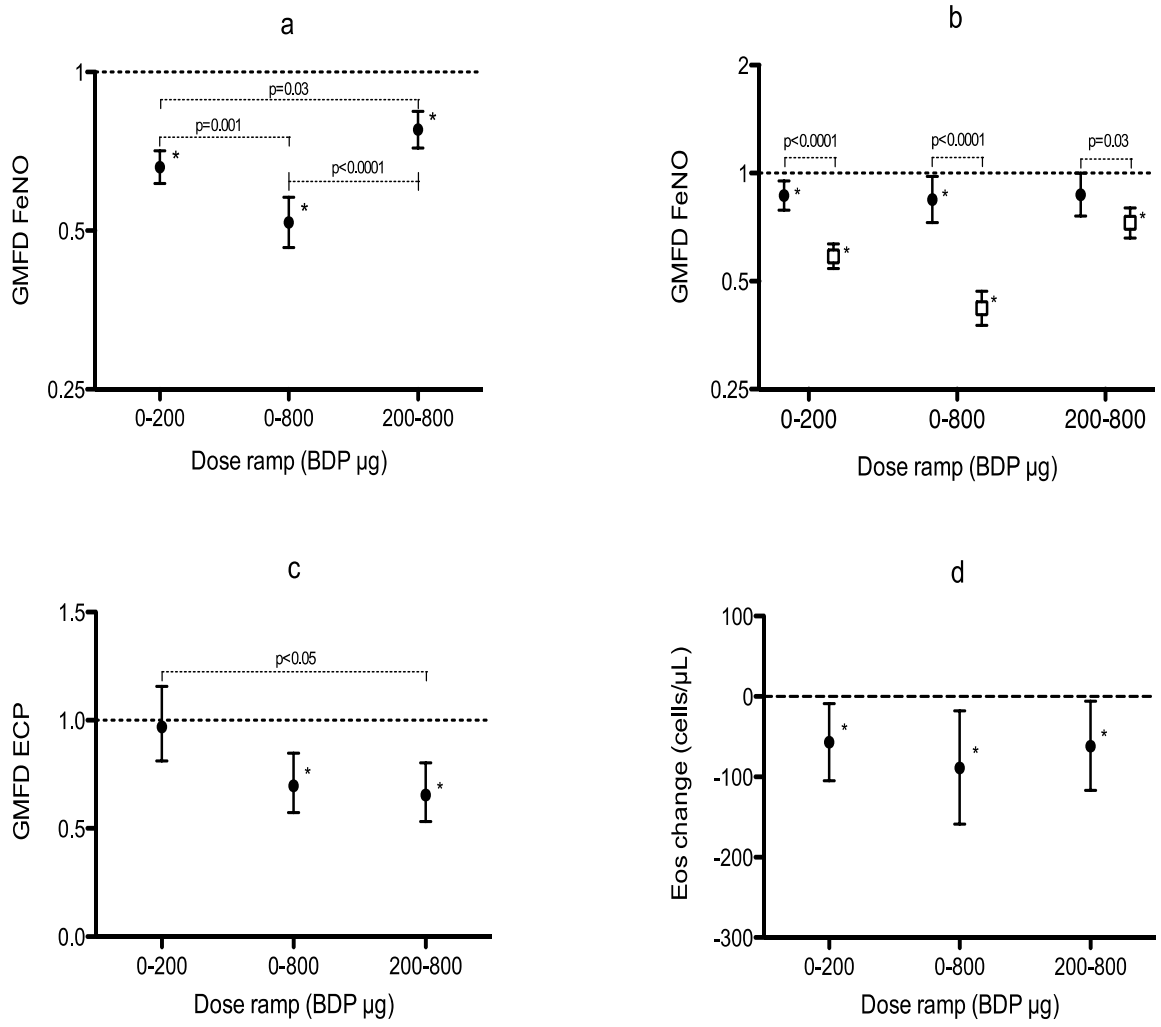
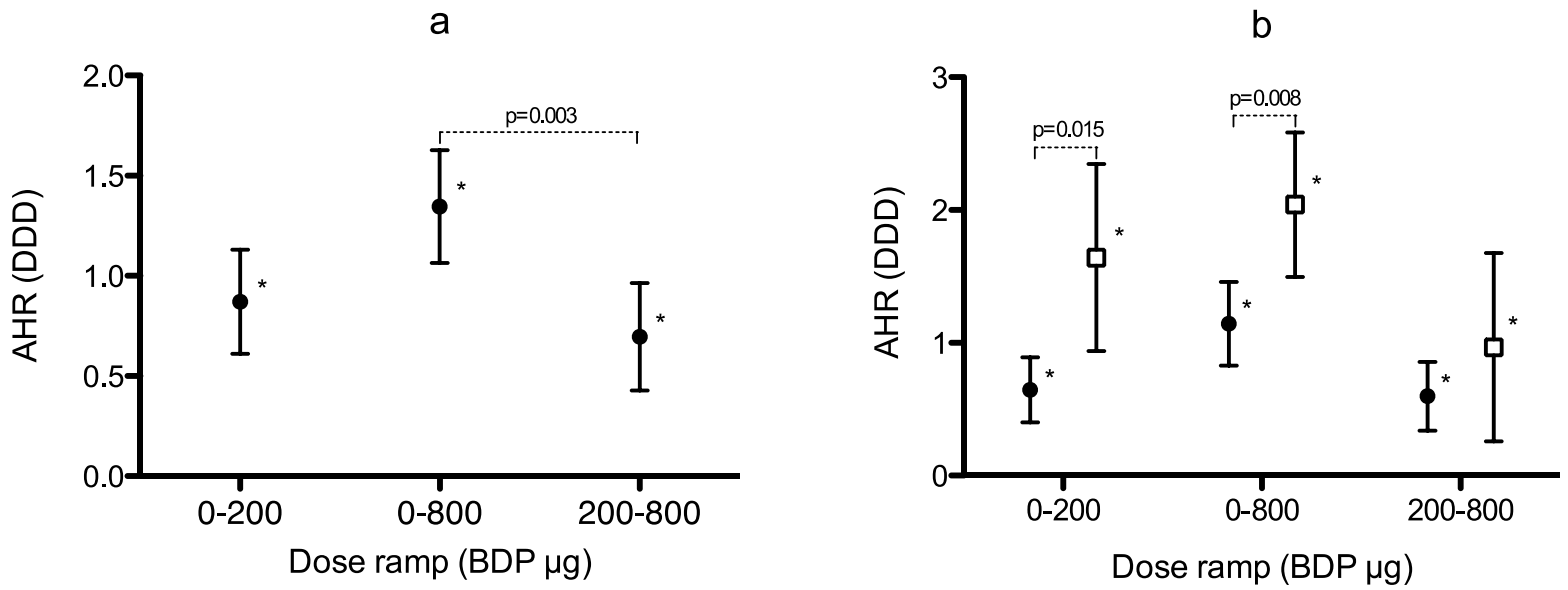

a
GMFD FeNO
1
0.5
0.25
p=0.03
p=0.001
p<0.0001
0-200
0-800
200-800
Dose ramp (BDP µg)
b
GMFD FeNO
2
1
0.5
0.25
p<0.0001
p<0.0001
p=0.03
0-200
0-800
200-800
Dose ramp (BDP µg)
c
GMFD ECP
1.5
1.0
0.5
0.0
p<0.05
0-200
0-800
200-800
Dose ramp (BDP µg)
d
Eos change (cells/µL)
100
0
-100
-200
-300
0-200
0-800
200-800
Dose ramp (BDP µg)

**Figure 3**


a
AHR (DDD)
2.0
1.5
1.0
0.5
0.0
p=0.003
*
*
*
0-200
0-800
200-800
Dose ramp (BDP µg)
b
AHR (DDD)
3
2
1
0
p=0.015
p=0.008
*
*
*
*
*
0-200
0-800
200-800
Dose ramp (BDP µg)